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AWARD NUMBER: DAMD17-03-1-0487

TITLE: Fusions of Breast Carcinoma and Dendritic Cells as a Vaccine for the Treatment of Metatastic Breast Cancer

PRINCIPAL INVESTIGATOR: Donald W. Kufe, M.D.
Baldev Vasir, Ph.D.
David Avigan, M.D.

CONTRACTING ORGANIZATION: Dana Farber Cancer Institute
Boston, MA 02115

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Department of Defense Grant # DAMD17-03-1-0487
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David Avigan, MD
Baldev Vasir, PhD
Donald Kufe, MD

Introduction

The overall objective of the project is to study the safety, immunologic response, and clinical effect of vaccination with dendritic cell (DC)/breast cancer fusions administered in conjunction with IL-12 in patients with metastatic breast cancer. DC/breast carcinoma fusion cells present a broad array of tumor-associated antigens in the context of DC-mediated costimulation. Fusion cells stimulate tumor specific immunity with the capacity to lyse autologous tumor cells. In clinical studies, vaccination with fusion cells was well tolerated, induced immunologic responses in a majority of patients, and results in disease regression in subset of patients. We postulated that administration of the vaccine in conjunction with IL-12 would further enhance vaccine response by promoting T cell activation.

In the first 3 years of the grant, we examined DC/breast carcinoma fusions with respect to their phenotypic characteristics as antigen presenting cells and their capacity to stimulate anti-tumor immunity. We demonstrated that DC/breast carcinoma fusions strongly express costimulatory, adhesion, and maturation markers as well as the stimulatory cytokines, IL-12 and IFNγ. In addition, fusion cells expressed CCR7 necessary for the migration of cells to sites of T cell traffic in the draining lymph nodes. In concert with these findings, fusions generated with immature and mature DCs potently stimulated CTL mediated lysis of autologous tumor targets.

In year 4 of the grant, we examined the T cell response to DC/breast carcinoma fusions with respect to the presence of activated and regulatory T cells. We demonstrated that DC/breast carcinoma fusions stimulate a mixed population of cells consisting of CD4/CD25/CD69 and CD4/CD25/Foxp3+ cells. The increased presence of regulatory cells was thought to potentially inhibit the in vivo efficacy of the fusion cell vaccine. As such, we have examined several strategies to bias the fusion-mediated T cell response towards activated cells. We have found that addition of IL-12, TLR7/8 agonists, CPG ODN, or IL-18 increase the relative presence of activated as compared to regulatory cells. Importantly, we have also found that DC/breast carcinoma fusion-induced

activation of autologous T cells and then stimulation with anti-CD3/CD28 results in a marked expansion of anti-tumor effector cells.

Body

Our clinical protocol had received approval by the FDA, NCI/CTEP (distributor of IL-12) and Dana-Farber/Harvard Cancer Center. We had also met the requirements as outlined in the DOD review process. However, during the protracted period of review, the availability of IL-12 was suspended for recertification, which significantly delayed the initiation of the clinical trial. We worked closely with Drs. Zweibel and Streicher at CTEP who have assumed control of the IL-12 stocks and have now completed the requisite potency testing for their release.

In the past year, we have been working with our DOD reviewer, Suzanne E. Dolney, to finalize DOD approval so that we can initiate the study. Our correspondence is summarized below:

1. Request for further information from DOD issued 3.4.09
2. Reponses to additional requests sent to DOD 3.5.09
3. DOD issued a protocol evaluation form on 3.16.09 allowing the protocol and consent to be submitted back to the IRB for final approval
4. On 5.15.09, the DOD provided the contact person for submitting the study's continuing review and approval
5. On 5.18.09, Continuing Review and approval was submitted to the DOD
6. On 6.16.09, the latest IRB approved version of the protocol and consent was sent to the DOD for review
7. On 6.23.09, the DOD requested CV information and the IRB correspondence for the latest version of the protocol and consent.
8. On 6.23.09, the requested CV information was sent to DOD
9. On 7.1.09, requested IRB correspondence for the latest version of the protocol and consent was sent
10. On 7.16.09, further changes were made to the protocol and consent
11. On 7.28.09, the NCI approval for the latest version of the protocol and consent was sent
12. On 8.5.09, the DOD issued Initial Approval for Protocol, "Vaccination of Patients With Breast Cancer With Dendritic Cell/Tumor Fusions and IL-12," Submitted by Donald W. Kufe, M.D., Dana-Farber Cancer Institute, Boston, MA, and David Avigan, MD, Beth Israel Deaconess Medical Center, Boston, MA, in Support of Proposal, "Fusions of Breast Carcinoma and Dendritic Cells as a Vaccine for the Treatment of Metastatic Breast Cancer," BB IND No. 8184, NCI Protocol No. 6040, DFCI Protocol No. 03-221, Proposal No. BC020048, Award No. DAMD17-03-1-0487, HRPO Log No. A-12181

Please see all approvals in the Appendix.

Key Research Accomplishments

During the past year, we have worked with the DOD to finalize the protocol. We are awaiting final approval to be obtained; we will resubmit the protocol to the FDA and our IRB for their approvals.

Reportable Outcomes

There are no reportable outcomes for the last year.

Conclusions

We are making progress in terms of working through the review requirements of the DOD, FDA, CTEP and our IRB and plan to activate the trial in the next 3 months.

Appendix:

Classification: **UNCLASSIFIED**

Caveats: NONE

SUBJECT: Initial Approval for Protocol, "Vaccination of Patients With Breast Cancer With Dendritic Cell/Tumor Fusions and IL-12," Submitted by Donald W. Kufe, M.D., Dana-Farber Cancer Institute, Boston, MA, and David Avigan, MD, Beth Israel Deaconess Medical Center, Boston, MA, in Support of Proposal, "Fusions of Breast Carcinoma and Dendritic Cells as a Vaccine for the Treatment of Metastatic Breast Cancer," BB IND No. 8184, NCI Protocol No. 6040, DFCI Protocol No. 03-221, Proposal No. BC020048, Award No. DAMD17-03-1-0487, HRPO Log No. A-12181

1. The subject protocol (Version 4 dated 24 October 2008) was approved by the Dana-Farber Cancer Institute (DFCI) Institutional Review Board (IRB) on 9 June 2009 and the National Cancer Institute (NCI) on 22 July 2009. This protocol was reviewed by the U.S. Army Medical Research and Materiel Command (USAMRMC) Office of Research Protections (ORP), Human Research Protections Office (HRPO) and found to comply with applicable Federal, DOD, U.S. Army, and USAMRMC human subjects protection requirements.

2. This greater than minimal risk study is approved for enrollment of up to 51 subjects.

3. Please note the following reporting obligations:

a. Major modifications to the research protocol and any modifications that could potentially increase risk to subjects must be submitted to the U. S. Army Medical Research and Materiel Command (USAMRMC) Office of Research Protections (ORP), Human Research Protections Office (HRPO) for approval prior to implementation. All other amendments must be submitted with the continuing review report to the HRPO for acceptance.

b. All unanticipated problems involving risks to subjects or others, serious adverse events related to study participation, and deaths related to study participation must be reported promptly to the HRPO.

c. Any deviation to the subject protocol that affects the safety or rights of the subject and/or integrity of the study data must be reported promptly to the HRPO.

d. All modifications, deviations, unanticipated problems, adverse events, and deaths must also be reported at the time of continuing review of the protocol.

e. A copy of the continuing review report approved by the DFCI IRB and NCI must be submitted to the HRPO as soon as possible after receipt of

approval. It appears the next continuing review by the DFCI IRB and NCI is due no later than 19 April 2010.

f. In addition, the current version of the protocol and consent form (if applicable) must be submitted along with the continuing review report and the DFCI IRB and NCI approval notices for continuation of the protocol.

g. The final study report submitted to the DFCI IRB and NCI, including a copy of any acknowledgement documentation and any supporting documents, must be submitted to the HRPO as soon as all documents become available.

4. Do not construe this correspondence as approval for any contract funding. Only the Contracting Officer or Grants Officer can authorize expenditure of funds. It is recommended that you contact the appropriate contract specialist or contracting officer regarding the expenditure of funds for your project.

5. The HRPO point of contact for this study is Suzanne E. Dolney, BSN, RN, Human Subjects Protection Scientist, at 301-619-6657/suzanne.dolney@us.army.mil.

LAURA RUSE BROSCH, RN, PhD
Director, Office of Research Protections
Human Research Protection Office
U.S. Army Medical Research and Materiel Command

Note: The official signed copy of this acceptance memo is housed with the protocol file at the Office of Research Protections, 504 Scott Street, Fort Detrick, MD 21702. Signed copies will be provided upon request.

Classification: **UNCLASSIFIED**

Caveats: NONE

Office for Human Research Studies
Dana Farber Cancer Institute
20 Overland Street
Boston, MA 02115
(617) 632-3029

Amendment: Notification of IRB Approval

DFCI Legacy #: 03-221

Date: 06/10/2009

To: David Avigan, MD

From: OHRS

Title of Protocol:	Vaccination of Patients with Breast Cancer with Dendritic Cell/Tumor Fusions and IL-12
Version/Number:	Version #4, 10/24/2008
IRB Amendment #:	8
IRB Review Type:	Full
IRB Approval Date:	06/09/2009
IRB Expiration Date:	04/19/2010

This Amendment to ongoing approved project has been reviewed and approved by the DFCI IRB, Assurance # FWA00001121. During the review of this Amendment to ongoing approved project, the IRB specifically considered (i) the risks and anticipated benefits, if any, to subjects; (ii) the selection of subjects; (iii) the procedures for securing and documenting informed consent; (iv) the safety of subjects; and (v) the privacy of subjects and confidentiality of the data.

Please note that if an IRB member had a conflict of interest with regard to the review of this project, that member left the room during the discussion and the vote on this project.

As Principal Investigator you are responsible for the following:

1. Submission in writing of any and all changes to this project (e.g., protocol, recruitment materials, consent form, study completion, etc.) to the IRB for review and approval prior to initiation of the change(s), except where necessary to eliminate apparent immediate hazards to the subject(s). Changes made to eliminate apparent immediate hazards to subjects must be reported to the IRB within 24 hours.
2. Submission in writing of any and all adverse event(s) that occur during the course of this project in accordance with the IRB's policy on adverse event reporting.
3. Submission in writing of any and all unanticipated problems involving risks to subjects or others.
4. Use of only IRB approved copies of the consent form(s), questionnaire(s), letter(s), advertisement(s), etc. in your research. Do not use expired consent forms.
5. Informing all physicians listed on the project of changes, adverse events, and unanticipated problems.
6. The following administrative conditions must be met prior to activation (i.e., accrual of subjects): **Other (DFCI)**

The IRB can and will terminate projects that are not in compliance with these requirements. Direct questions, correspondence and forms (e.g., continuing reviews, amendments, adverse events, safety reports) to OHRS Office, 617-632-3029.

Office for Human Research Studies
Dana Farber Cancer Institute
20 Overland Street
Boston, MA 02115
(617) 632-3029

cc:
David E Avigan, MD
Susan Schumer, MD
James L Levine, MD
Corrine Zarwan, MD
Lowell E. Schnipper, MD
Donald W. Kufe, MD
Robin M Joyce, MD
David McDermott, MD
Jacalyn Rosenblatt, MD
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Hallie Kasper, RN
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Donna Fitzgerald
Katharine Conway, NP
Meredith Regan
Uma Akella
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Department of Health & Human Services **Public Health Service**

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

Reference Number ***P6040#A02PAMDREVW01***

JUL 22 2009

Date:
NCI Protocol #: ***6040***
Local Document Number: ***03-221***
Local Change #: ***VERSION 5***
Amendment #: ***2***
Version Date: ***06/11/2009***
Principal Investigator: ***David E. Avigan,* M.D.**

***Donald W. Kufe,* M.D.**
Dana-Farber Cancer Institute
44 Binney Street
Boston, MA 02115

Dear ***Dr. Kufe:***

An amendment to your Protocol, NCI #***6040***, entitled,*" **Vaccination of Patients with Breast Cancer with Dendritic Cell/Tumor Fusions and IL-12"***, was received by the Cancer Therapy Evaluation Program of the Division of Cancer Treatment and Diagnosis, National Cancer Institute on ***07/16/2009***.

The Amendment has been reviewed with the following status:

___✓___ Approved as written.
_____ Approved with recommendations. See attached review.
_____ Disapproved. **

***Please note: CTEP amendment approval is all-or-nothing. ALL changes submitted with an amendment that has been disapproved must be resubmitted for approval prior to implementation.*

HIPAA Disclaimer: Decisions about the applicability and implementation of the HIPAA Privacy Rule reside with the researcher and his/her institution. Therefore, the Cancer Therapy Evaluation Program will NOT be reviewing documents for compliance with this regulation. If informed consent forms contain language pertaining to HIPAA authorizations, the informed consent components will be assessed for compliance with the Common Rule and FDA regulations, and the confidentiality section will be reviewed for the listing of collaborators who will have access to the identifiable information.

Sincerely,

***Howard Z. Streicher*, M.D.**
Senior Investigator
Investigational Drug Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute